Efficacy of long-term sublingual-oral immunotherapy in allergic rhinitis

L'efficacia dell'immunoterapia orale-sublinguale nella rinite allergica

C. CINGI, S. AYNACI, H. CAKLI, E. CINGI, E. ÖZÜDOGRU, C. KEÇIK, F. ALTIN, C. BAL[1]
ENT Department; [1] Biostatistics Department,
Osmangazi University, Medical Faculty, Eskisehir, Turkey

Key words

Nose • Allergic rhinitis • Oral immunotherapy • Skin test • Specific IgE

Parole chiave

Naso • Rinite allergica • Immunoterapia orale • Testi dermatologici • Specifiche IgE

Summary

Aim of the study was to evaluate the clinical efficacy of sublingual-oral immunotherapy in allergic rhinitis induced by various allergens and to demonstrate its effects using objective methods such as skin prick tests and specific IgE analysis. The first 100 patients diagnosed with allergic rhinitis and treated with sublingual-oral immunotherapy took part in the study and were followed for 2 years. Baseline findings were statistically compared with data obtained at the end of the study period. All symptoms including nasal discharge, sneezing, nasal congestion, and itching, as well as all clinical findings, including lower turbinate colour, turbinate congestion, and nasal discharge, observed by the physician, were significantly decreased after sublingual-oral treatment for two years ($p < 0.001$). A significant reduction in skin test reactivity was found when the initial and the final tests were compared. The difference between before and after treatment levels of specific IgE levels for *D. pteronyssinus*, *D. farinea*, and grasses were significant ($p < 0.001$), but were not significant for cereals ($p = 679$ ns). As far as concerns the correlation between the recovery of clinical findings and age, as well as the correlation between the recovery of clinical findings and sex, neither of these were statistically significant (age: $r = -0.076$, $p = 0.453$, sex: $r = -0.004$, $p = 0.97$). The efficacy of the treatment, determined by means of symptom evaluations, was higher than expected in our study. A certain effect of this recovery might be due to the placebo effect, but it is supported by the improvement in skin tests and specific IgE levels.

Riassunto

Lo scopo di questo studio è valutare l'efficacia clinica dell'immunoterapia orale-sublinguale nelle riniti allergiche causate da vari allergeni e dimostrare i suoi effetti con metodi obiettivi come i test dermatologici e il dosaggio di IgE specifiche. Cento pazienti, con diagnosi di rinite allergica e trattati con immunoterapia orale-sublinguale, hanno preso parte a questo studio e sono stati seguiti per due anni. I dati osservati, al momento della diagnosi, sono stati statisticamente confrontati con i dati ottenuti alla fine del periodo di studio. I sintomi, fra cui rinorrea, starnuti, congestione nasale, prurito, così come tutti i dati clinici obiettivi osservati dai medici, sono diminuiti dopo il trattamento orale-sublinguale per due anni ($p < 0,0001$). Il confronto fra i risultati iniziali e finali dei test dimostrano una riduzione significativa della reattività. Le differenze fra prima e dopo il trattamento relative al livello di IgE specifiche per D. pteronyssinus, D. farinea e per le erbe sono significative ($p < 0,0001$), però non sono significative per i cereali ($p = 679$ ns.) Né la correlazione fra i risultati clinici e l'età, né la correlazione fra i risultati e il sesso sono risultate statisticamente significative (età: r: 0,0076, $p = 0,453$; sesso: r: 0,004, $p = 0,97$). Il miglioramento dei sintomi, rispetto al periodo antecedente al trattamento, potrebbe essere legato anche all'effetto placebo, però il miglioramento dei test dermatologici e dei livelli di IgE specifiche garantisce l'affidabilità dei risultati osservati.

Introduction

Allergic rhinitis is a global health problem affecting at least 10 to 25% of the population. In the treatment of allergic disorders, specific immunotherapy occupies a central role as the only currently available causal method of treatment [1]. The concept of specific desensitization clinically leads to reducing sensitivity and reducing symptoms. The traditional subcutaneous route has proven to be effective but poor compliance can limit its wide use [2]. Furthermore, the possibility of important side-effects leads allergists to investigate new routes. Another issue is the agreement of allergists that subcutaneous immunotherapy needs to be performed in hospitals or well-equipped outpatient units by trained professionals. These concerns have led allergists to investigate the oral route. Two different routes of administration, such as sublingual-spit and sublingual-swallow methods have been defined. In the former, the allergenic extract is retained in the

mouth for a certain period of time, with the assumption that total absorption will take place at oral mucous membrane level and then the patient spits it out. Efficacy was observed in some studies with certain allergens [1]. The latter is the combination of oral and sublingual immunotherapy. The allergenic extract is retained in the mouth for a predetermined period of time and then swallowed. There are also successful reports obtained with this method as well as unsuccessful results [1 3-5].

The scientific basis for oral immunotherapy stems from the high number of immunocompetent cells located in the intestinal lymph nodes [6]. The original rationale for administering immunotherapy sublingually was achieving a prompt and rapid absorption of the vaccine to avoid possible degradation in the gastrointestinal tract [7].

The aim of this study is to evaluate the clinical efficacy of sublingual-oral immunotherapy in allergic rhinitis induced by various allergens and to demonstrate its effects by objective methods such as skin prick tests and specific IgE analysis.

Material and Methods

The first 100 patients diagnosed with allergic rhinitis and treated with sublingual-oral immunotherapy were included in this study and followed for 2 years. A previously prepared form was used for patient follow-up for this particular study.

Initially, routine clinical ear nose and throat (ENT) examinations were performed in all patients, in the outpatient setting. The patients diagnosed with allergic rhinitis clinically, were then referred to the ENT Allergy Unit. Follow-up was performed, periodically, by the same physicians. The baseline findings were statistically compared to the data obtained at the end of the 2-year period. Residential characteristics were evaluated, and allergy in other members of the family was also recorded.

Symptom scores

In order to evaluate, and statistically compare, symptoms such as nasal discharge, sneezing, nasal congestion, and itching, these were quantified and coded as: 0 = none, 1 = mild, 2 = moderate, 3 = severe [8]. The same procedure was performed at each control.

Clinical findings

Clinical findings such as lower turbinate colour, turbinate congestion, and nasal discharge observed by the physician were quantified and coded as: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Statistical analysis was performed using the initial and final data obtained.

Skin-prick tests

Skin tests were performed with the application of a small amount of concentrated allergen on the skin, then pricking the skin through the solution into the epidermal layer with a 1 mm Prick test lancet. Grading of the skin reaction is based on the relation of the size of the skin wheal and flare reaction compared to the positive control (histamine solution), reading the reaction after 15 minutes. Antigen-induced wheals larger than the histamine control are read as 4+, same as with the control being 3+, reactions two thirds the control as 2+, and reactions one third the control as 1+ [9]. *Dermatophagoides pteronyssinus (D1)*, *Dermatophagoides farinae (D2)*, grass/cereal mixture, weed mixture, tree mixture, fungus mixture positive and negative controls were included in all tests. The allergens used were obtained from Allergopharma, Germany.

Blood sampling and analysis

Levels of serum specific IgE were determined by Fluoroenzyme-Immunoassay (FEIA) (Pharmacia, Upjohn, Sweden) in the Clinical Microbiology Department. Allergy Section. of Osmangazi University Hospital, Eskisehir, Turkey. The specific IgE levels tested against *D1, D2*, grass mixture, weed mixture, tree mixture, and fungus mixture. Specific IgE levels were classed as 0, 1, 2, 3, 4, 5 and 6. Values lower than 1.43 SU/ml are indicated as Class 0, values between 1.43-4 SU/ml as Class 1, values between 4-20 SU/ml as Class 2, values between 20-100 SU/ml as Class 3, values between 100-300 SU/ml as Class 4, values between 300-500 SU/ml as Class 5 and values > 500 as Class 6.

Immunotherapy

Immunotherapy consisted of two phases, namely, initiation and maintenance. The initiation kit comprised 3 vials of different dosage between 1 IR/ml to 100 IR/ml. Patients received increasing doses starting with one drop from the first vial (1 IR/ml). The dose was increased by one drop every day such as 3 drops on the third day, four drops on the fourth day etc. When a dosage of 28 drops on the 28th day was reached, the same process was repeated for the second vial (10 IR/ml) and then the third vial (100 IR/ml). When a dosage of 28 drops from vial 3 was reached on the 84th day, maintenance therapy, consisting of 28 drops of 100 IR/ml, was given every other day, until the end of the 2-year period. Patients were instructed to take the drops in the morning before breakfast. The drops were kept in the mouth for at least two minutes and then swallowed [10]. The allergens used were obtained from Allergopharma, Germany.

Immunotherapy was administered as a single allergen vaccine in 38 cases, two vaccines in 40 cases and as three allergen vaccines in 22 cases.

Classifying them according to allergens: 53 patients

took D1 + D2 50%, 54 took grasses and cereals mixture, 10 took grasses, 25 took trees 1 mixture, 22 took trees 2 mixture, 12 took fungi mixture and 4 patients took weed mixture.

Statistical analysis

Pearson chi-square, (χ^2_P), Yates chi-square (χ^2_Y, continuity correction), Fisher exact test (χ^2_F), Z test (normal approximation), Wilcoxon Signed Ranks test and Spearman correlation analysis (rS) were used in the statistical analyses. Analyses were performed by SPSS 11.5. $p \leq 0.05$ was considered statistically significant [11].

Results

The study population comprised 44 males and 56 females (mean age 30.04 ± 1.10 years, range 17-39). Of these patients, 89 lived in the city while 11 lived in rural areas. A total of 69 patients lived in apartment buildings whereas the remainder lived in a house with a garden. A positive family background for allergic diseases was reported in 30 cases.

All cases were classified as persistent and moderate-severe. Although 40 of the patients were accepted as seasonal and the remainder were perennial, according to the previous classification. The evaluation and comparison of symptoms before and after the treatment, such as nasal discharge, sneezing, nasal congestion, and itching are given in Table I.

All symptoms were significantly decreased after sublingual-oral treatment for two years ($p < 0.001$). Neither the correlation between the decrease of symptoms and age nor the correlation between the decrease of symptoms and sex were statistically significant (age: r = 0.071, p = 0.484, sex: r = -0.158, p = 0.117).

Evaluation and comparison of severity of the clinical findings before and after treatment, such as nasal discharge and nasal congestion, are given in Table II.

All examination findings were found to have significantly recovered after sublingual-oral treatment for two years ($p < 0.001$). Neither the correlation between the recovery of clinical findings and age, nor the correlation between the recovery of clinical findings and sex were statistically significant (age: r = -0.076, p = 0.453, sex: r = -0.004, p = 0.97).

When the results of prick tests were evaluated, in 22 patients a positive result to a single allergen was detected; in 34 patients to 2 allergens; in 24 patients to 3 allergens, in 12 patients to 4 allergens, in 6 patients to 5 allergens, in one patient to 6 allergens, in one patient to 7 allergens. Prick test results before and after treatment are given in Table III.

Specific IgE levels for D1 before and after treatment are given in Table IV.

The difference between before and after treatment levels of specific IgE levels for D1, D2, grasses were significant ($p < 0.001$).

Specific IgE levels for D2 and grass before and after treatment are given in Tables V and VI.

Specific IgE levels for Fungimixture before and after treatment are given in Table VII. The difference between before and after treatment levels of specific IgE levels for Fungimixture was significant (p = 0.023), but was not significant for cereals (p = 679 ns).

No systemic reactions were recorded during the treatment. Only oral and labial itching were reported by 5 patients.

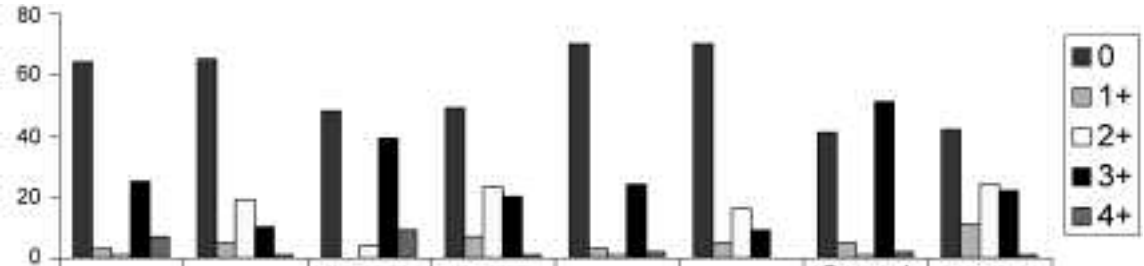
Table I. Symptoms of patients before and after treatment.

	Symptoms							
	Nasal discharge		Sneezing		Nasal itching		Nasal obstruction	
	Before	After	Before	After	Before	After	Before	After
None (0)	2	10	3	12	1	18	6	25
Mild (1)	8	27	4	30	14	38	37	52
Moderate (2)	30	46	38	51	46	38	46	22
Severe (3)	60	17	55	7	39	6	11	1
Total (n)	100	100	100	100	100	100	100	100

Table II. Clinical findings before and after treatment.

	Clinical findings			
	Congestion		Nasal discharge	
	Before	After	Before	After
None (0)	3	28	27	68
Mild (1)	51	54	44	27
Moderate (2)	42	18	29	5
Severe (3)	4	0	0	0
Total (n)	100	100	100	100

Table III. Skin prick test results before and after treatment.



	D. Farinae before treatment	D. Farinae after treatment	D. Pteronys-sinus before treatment	D. Pteronys-sinus after treatment	Grass polen before treatment	Grass polen after treatment	Grass and cereals mixture before treatment	Grass and cereals mixture after treatment
0	64	65	48	49	70	70	41	42
1+	3	5	0	7	3	5	5	11
2+	1	19	4	23	1	16	1	24
3+	25	10	39	20	24	9	51	22
4+	7	1	9	1	2	0	2	1

Table IV. Specific IgE levels for D1 before and after treatment.

	Specific IgE levels for D1 after treatment (kUA/l)								Total (n)
		0	**1**	**2**	**3**	**4**	**5**	**6**	
Specific	**0**	**7**	0	0	0	0	0	0	7
IgE levels	**1**	0	**2**	0	0	0	0	0	2
for D1	**2**	0	3	**4**	0	0	0	0	7
before	**3**	0	0	5	**2**	0	0	0	7
treatment	**4**	0	1	3	13	**3**	0	1	21
(kUA/l)	**5**	0	0	1	0	4	**1**	0	6
	6	0	0	0	0	0	3	**0**	3
Total (n)		7	6	13	15	7	4	1	**53**

Table V. Specific IgE levels for D2 before and after treatment.

	Specific IgE levels for D1 after treatment (kUA/l)								Total (n)
		0	**1**	**2**	**3**	**4**	**5**	**6**	
Specific	**0**	**12**	0	0	0	1	0	0	13
IgE levels	**1**	0	**3**	0	0	0	0	0	3
for D2	**2**	2	2	**6**	0	0	0	0	10
before	**3**	0	0	1	**3**	0	0	0	4
treatment	**4**	0	0	6	7	**0**	1	0	14
(kUA/l)	**5**	0	0	1	0	5	**2**	0	8
	6	0	0	0	0	0	1	**0**	1
Total (n)		14	5	14	10	6	4	0	**53**

Table VI. Specific IgE levels for grass before and after treatment.

	Specific IgE levels for D1 after treatment (kUA/l)								Total (n)
		0	**1**	**2**	**3**	**4**	**5**		
Specific	**0**	**16**	0	0	0	0	0	16	
IgE levels	**1**	0	**4**	1	0	0	0	5	
for grass	**2**	1	2	**4**	0	0	0	7	
before	**3**	0	3	10	**6**	1	0	20	
treatment	**4**	0	0	1	5	**2**	0	8	
(kUA/l)	**5**	0	0	0	0	8	**0**	8	
Total (n)		17	9	16	11	11	0	**64**	

Table VII. Specific IgE levels for Fungimixture before and after treatment.

	Specific IgE levels for D1 after treatment (kUA/l)								Total (n)
		0	**2**	**3**	**4**	**5**	**6**		
Specific IgE	**0**	**4**	0	0	0	0	0	4	
levels for	**2**	1	**0**	0	0	0	0	1	
Fungimixture	**3**	0	2	**1**	0	0	0	3	
before	**4**	0	0	0	**1**	0	0	1	
treatment	**5**	0	0	1	0	**0**	0	1	
(kUA/l)	**6**	0	0	0	2	0	**0**	2	
Total (n)		**5**	**2**	**2**	**3**	**0**	**0**	**12**	

Discussion

Several studies have been performed on allergen specific immunotherapy during the last few decades [7]. Subcutaneous injection immunotherapy is a method which has been used for many years, in many countries, but poor compliance has limited the applicability of this treatment method. Furthermore, systemic side-effects restrict the widespread use of subcutaneous immunotherapy. It has been used for 14 years in our clinic. Although many patients have continued their therapy regimen, we observed that many patients showed poor compliance. Therefore, new methods of local application have been sought.

The concept of "local immunotherapy" includes all non-subcutaneous forms of specific immunotherapy. Oral, sublingual, nasal and bronchial administration of allergen extracts is regarded as local immunotherapy [4 5]. These routes have been variously referred to as: alternative, non-parenteral, non-injection or local routes. Mucosal membranes of the respiratory and intestinal tracts, which represent a vast area of contact with the environment, are exposed daily to antigenic substances, which induce specific humoral as well as cell-mediated immune responses not only at the site of the stimulation-mucosa-associated lymphoid tissues, but also in the draining lymph nodes, spleen and bone marrow [12]. This idea encourages the attempt to investigate the oral route. Fanta et al. [13] after their sublingual spit immunotherapy investigation concluded that sublingual treatment leads to systemic changes in immunoreactivity to the administered allergen. The sublingual-oral approach seems to offer the advantage both of sublingual and intestinal administration, thus it was the preferred method in our study. Compliance of our patients to oral immunotherapy was very good, especially in those patients who had previously used subcutaneous injection immunotherapy before willingly switching to the sublingual-oral form.

The efficacy of the treatment, by means of symptom evaluations was, maybe, more than that expected, in our study. We found a very high recovery rate, a cer-

tain effect of which might be due to the placebo effect, but it is supported by the improvement in skin tests and specific IgE levels.

A significant reduction in skin test reactivity was found in our study when we compared the initial and the final tests. Tari et al. [8] had previously described a similar result, but according to some reports concerning sublingual immunotherapy its effect was based on subjective clinical parameters but not on objective methods [14]. In our case, a decrease of skin reactivity was obtained with mites, grass and cereal mixtures, tree pollens 1, but not with tree pollens 2, weeds and fungi mixture. In our opinion, the clinical outcome is more important than objective methods.

North American allergists tend to use multiple allergen vaccines, whereas Northern Europeans often prefer to use single allergen vaccines [15]. In our study group, we used single allergen extracts in 38 patients and multiple allergen extracts in 62.

The only side-effect was oral and labial itching, after taking the dose, in 5 patients. Two patients reported nausea in the morning but its cause was uncertain and then accepted as not related to immunotherapy since it also occurred prior to treatment. The most frequently reported side-effects, in previous studies, were similar, such as itching in the throat, nose and oral region. The other most frequent side-effects are nausea, vomiting and abdominal pain [1 16 17].

The efficacy of the treatment, determined by means of symptom evaluations, was more than that expected, in our study. A certain effect of this recovery might be due to its placebo effect, but it is supported by the improvement in skin tests and specific IgE levels. When we compared the specific IgE values numerically, a significant decrease was observed. The decrease in specific IgE values is a good objective criterion in allergic rhinitis which is usually evaluated clinically. In our opinion, being under continuous treatment, both at home and in our allergy unit, influenced our patients positively.

Further research will lead to more efficient and reliable immunotherapy modalities, in the near future.

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■ Address for correspondence: Prof. C. Cingi, Visne Evleri 10/3, (26020) Eskisehir, Turkey - Fax +90 222 2393774 - E-mail: ccingi@ogu.edu.tr